Psychological distress and risk of myocardial infarction and stroke in the 45 and Up Study: a 1 prospective cohort study

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Short title: Psychological distress and MI and stroke risk

Caroline A Jackson (PhD)*[1,2], Cathie LM Sudlow (DPhil)[1,3], Gita D Mishra (PhD)[2]

[1]Usher Institute of Population Health Sciences and Informatics
University of Edinburgh
Nine Bioquarter, 9 Little France Road
Edinburgh, EH16 4UX

[2]School of Public Health
University of Queensland

[3]Centre for Clinical Brain Sciences
University of Edinburgh

*Corresponding author contact details:
Email: caroline.jackson@ed.ac.uk

Tel: +44 (0) 1316517872

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ABSTRACT

Background The interplay between mental and physical health remains poorly understood. We investigated whether psychological distress is associated with risk of myocardial infarction (MI) and stroke in a population-based prospective study.

Methods and Results We included participants without prior stroke/MI from the New South Wales 45 and Up Study. We categorised baseline psychological distress as low, medium, and high/very high on the 10-item Kessler Psychological Distress Scale and identified stroke and MI through linkage to hospital admission and mortality records. We obtained sex and age-stratified adjusted and unadjusted hazard ratios (HRs) for the association between psychological distress and MI and stroke. We investigated for interaction between psychological distress and each of age and sex.

Among 221,677 participants 16.2% and 7.3% had moderate and high/very high psychological distress at recruitment, respectively. During 4.7 ± SD 0.98 years of follow-up, 4573 MIs and 2421 strokes occurred. Absolute risk of MI and stroke increased with increasing psychological distress level. In men aged 45-79, high/very high versus low psychological distress was associated with a 30% increased risk of MI (fully adjusted HRs 1.30, 95% CI 1.12 to 1.51), with weaker estimates in those aged ≥80 years. Among women, high/very high psychological distress was associated with an 18% increased risk of MI (adjusted HR 1.18, 95% CI 0.99, 1.42) with similar findings across age-groups. In the 45-79 years age group, high/very high psychological distress and male sex had a supra-additive effect on MI risk. Similar estimates were observed for stroke, with high/very high psychological distress associated with a 24% and 44% increased stroke risk in men and women, respectively, with no evidence of interaction with age or sex.

Conclusion Psychological distress has a strong, dose-dependent, positive association with MI and stroke in men and women, despite adjustment for a wide range of confounders.

INTRODUCTION

Cardiovascular and cerebrovascular disease (collectively referred to here as CVD) are leading causes of mortality and morbidity worldwide.[1, 2] Mental disorders are a similarly important global public health problem, with depression and anxiety disorders listed second and ninth, respectively, in the top 20 causes of global years lived with disability.[2] The growing dual burden of CVD and mental disorders is of particular importance given the increasingly recognised, yet poorly understood, interplay between the two.[3, 4]

Common mental disorders such as depression and anxiety, or measures of their symptoms, are thought to be associated with an increased risk of coronary heart disease and stroke, but meta-analyses have found substantial heterogeneity between studies and inconsistency in findings.[5-8] Controversy persists as to whether common mental disorders or their symptoms play an independent aetiological role in the development of CVD, with the potential for residual confounding being a recurrent criticism of existing studies. Studies which define depression or anxiety based on a clinical diagnosis include a selected population, since they include those people who have sought or have access to healthcare for their mental health problems. An alternative approach, often used in population-based epidemiological studies, is to measure self-reported mental health problems, which somewhat reduces this selection bias and may improve generalisability of findings to the whole population setting. Some measures, such as the Centre for Epidemiological Studies Depression (CESD) scale seek to measure depressive symptoms only, whereas others, such as the Kessler psychological distress scale, measure non-specific psychological distress, but with a focus on depression and anxiety. Few studies have investigated the association between psychological distress and CVD occurrence and have generally examined CVD mortality[9-13] and not incidence. Existing studies which have reported on CVD incidence are limited by small size, incomplete adjustment for potential confounders, heterogeneous psychological distress measures and inconsistent findings.[14-19] Furthermore, studies have rarely reported sex-specific associations. The pathophysiology of psychological distress may differ between men and women, with changes in

hormone levels throughout the life-course playing a potentially important aetiological role in women.[20] Also, sex differences in treatment-seeking behaviour for, and/or specific treatment of psychological distress might lead to differential associations with CVD risk. Similarly, it is unclear whether the association between psychological distress and CVD risk persists within all age-groups. It is therefore prudent to explore differential demographic effects when relating psychological measures to physical disease.

To address these gaps, we investigated the association between psychological distress and incidence of myocardial infarction (MI) and stroke, by sex and age in a large prospective cohort study.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure since access to the data is only via approved application by the study investigators.

Study population

We included participants from the Sax Institute's 45 and Up Study, a prospective cohort from the New South Wales (NSW), Australia, general population aged 45 years or over, recruited in 2006-2009. Recruitment methods are described in detail elsewhere.[21] Briefly, potential participants were randomly sampled from the Department of Human Services (formerly Medicare Australia) database and mailed a self-administered questionnaire and information leaflet. Participants consented to follow-up, including linkage to routinely collected health datasets. For this study, the cohort was linked to the NSW Admitted Patient Data Collection, the Australian Capital Territory (ACT) Admitted Patient Collection and the Australian Bureau of Statistics Death Data, with linkage performed by the Centre for Health Record Linkage.[22] We excluded participants with a previous hospitalised stroke or MI record or self-reported stroke, MI or angina at baseline (since participants were asked about prior MI or angina within a single question).

The conduct of the 45 and Up Study was approved by the University of NSW Human Research Ethics Committee. Ethical approval for the present study was obtained from the NSW Population and Health Services Research Ethics Committee, the ACT Health Human Research Ethics Committee and the University of Queensland Institutional Human Research Ethics Committee.

Psychological distress

Psychological distress was measured at baseline using the self-administered 10-item Kessler psychological distress (K10) scale[23], a widely used screening tool that measures symptoms of psychological distress in the previous four weeks (Table 1). The K10 scale has high construct and factorial validity[23, 24] and has been shown to have high validity when evaluated against the gold standard of Structured Clinical Interview for DSM-IV disorders, especially mood and anxiety disorders.[25-27] We modelled psychological distress as a categorical variable since K10 scores were not normally distributed and heavily skewed, with many people reporting little or no psychological distress. We created low (scores of ≤15), moderate (16-21), high (22-29) and very high (30-50) distress groups, in line with categorisation used in Australian Bureau of Statistics surveys.[28] We combined the two latter categories, given the relatively low numbers in the highest groups.

Table 1 Component questions used in the 10-item Kessler Psychological distress scale and accompanying scoring system

'During the past 4 weeks, about how often did you feel':	Respondents selected 1 of 5 possible responses for each question: [score given]*	
tired out for no good reason?		
nervous?		
so nervous that nothing could calm you down?	None of the time:	[1]
hopeless?	A little of the time:	[2]
restless or fidgety?	Some of the time:	[3]
so restless that you could not sit still?	Most of the time:	[4]
depressed?	All of the time:	[5]
that everything was an effort?		
so sad that nothing could cheer you up?		
worthless?		
*Minimum total score = 10; maximum total score = 50		

Myocardial infarction and stroke

We identified incident MI and stroke from hospital admission discharge records and mortality records, defining MI using ICD-10 I21 and stroke using I60, I61, I63 and I64. These codes could appear either in the primary or secondary diagnosis/cause of death fields of hospital admission or mortality records. For analyses of pathological stroke types, ischaemic stroke was defined using I63 and I64 (since the majority of 'undetermined' strokes coded as I64 will be ischaemic),[29] and haemorrhagic stroke by I60 and I61.

Covariates

Definitions of covariates are given in supplementary Table 1. We adjusted for: sociodemographic factors (marital status, geographical remoteness, area-based deprivation, highest attained education level and average annual household income); lifestyle factors (body mass index (BMI); smoking status; alcohol intake; physical activity; daily fruit and vegetable consumption; and weekly fish intake); physiological factors and family history (self-reported history of hypertension, heart disease and diabetes, treated cholesterol in the past month, family history of heart disease or stroke and baseline physical comorbidity based on a modified Charlson comorbidity index[30] using hospital admission data in the five years prior to recruitment); and, among women, reproductive factors.

Statistical analyses

We performed analyses using Stata version 12. We summarised baseline characteristics by psychological distress and stroke occurrence and compared characteristics of included versus excluded participants (i.e., those without complete information on psychological distress).

Missing data and multiple imputation

The frequency of missing values was less than 5% for almost all covariates. However, due to wide dispersion of missingness, overall, 37% of men and 50% of women had missing values for at least one variable. We therefore used multiple imputation by chained equations to impute missing values of included covariates, performing 37 imputations for men and 50 for women.[31] We imputed data separately for men and women since we included sex-specific variables for women in our analyses.

Survival analyses

We created Kaplan-Meier plots of probability of survival free of each of stroke and MI for psychological distress categories, censoring for date of stroke event, non-stroke death and end of follow-up (31st Dec 2012), using age in years as the time scale. The proportional hazards assumption was violated for MI among men but not women. Thus, among men, the effect of psychological distress was not constant by age. As shown in supplementary Figure 1, the effect of moderate or high/very high psychological distress attenuated among those aged 80 years or over at baseline, with the gap between the survival curves narrowing. We therefore stratified by baseline age and report on the association between psychological distress and MI for each age group separately (ages 45-79 and ≥80), after confirming that the proportional hazards assumption was not violated within these two age groups. There was no violation of the proportional hazards assumption by psychological distress for the stroke model and no clear violation by any covariate included in the MI or stroke models.

We used Cox regression to obtain sex-specific unadjusted and serially adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between psychological distress and each of MI and stroke.

The primary analysis was performed following multiple imputation. We also performed a complete-case analysis (presented in supplementary material). As depicted simplistically in part A of Figure 1, there are multiple pathways through which psychological distress might lead to an increased risk of CVD. A number of these factors might also confound the association (as shown in part B of Figure 1). Since the K10 scale asks about psychological distress in the past four weeks, with information on covariates collected at baseline only, we treated all covariates as common sources (confounders) in our analyses and adjusted for them. Since some of these covariates might actually lie on a possible causal pathway between psychological distress and CVD, we acknowledge that this assumption may not be valid and discuss the implications of this in our discussion.

We investigated for interaction between psychological distress and sex on MI and stroke risk among participants aged 45-79 and 80 years or over at baseline. Within men and women separately, we also investigated for interaction between psychological distress and age on MI and stroke risk. We investigated interaction on the multiplicative scale by adding interaction terms to the age-adjusted models. Since additive (i.e. biological) interaction is more important for understanding population health, we also investigated interaction on the additive scale, by calculating the relative excess risk of interaction (RERI) and synergy index with accompanying 95% CIs.[32]

In subgroup analyses, we stratified by pathological stroke type.

This article was written in accordance with the STROBE statement.[33]

RESULTS

Among 267,019 participants, 248,462 were eligible for inclusion. After excluding those with missing information on psychological distress, we included 221,677 participants (Figure 2). Compared to included participants, excluded participants were older and more likely to be: female; of lower SES; and less healthy (supplementary Table 2). We included 102,039 men and 119,638 women (mean age 62.2 ± 10.5 and 60.2 ± 10.2, respectively). Psychological distress was more common in women than men (17.3% versus 14.8% for moderate distress and 8.1% versus 6.3% for high/very high distress, respectively; p <0.001) and more common in younger age groups for both men and women (p<0.001 for both sexes). Increasing psychological distress was also associated with lower SES, poorer lifestyle, clinical stroke risk factors, and among women, reproductive factors (Table 2). Similarly, most characteristics were associated with MI and stroke occurrence. Cross-tabulations of baseline characteristics and psychological distress stratified by sex and of baseline characteristics by MI and stroke are given in supplementary Tables 3-5.

Psychological distress and absolute risk of MI and stroke

The follow-up period was almost identical for the stroke and MI analyses. During a mean follow-up of 4.70 (± SD 0.98) years, 4573 MIs and 2421 strokes occurred. Absolute age standardised MI and

stroke risk was generally higher among men than women and increased with increasing psychological distress level (Table 3). When stratifying by age, this pattern persisted for MI incidence among men aged under 80 years at baseline, but not those aged 80 years or over (Figure 3a). In the latter group, MI incidence was broadly similar across levels of psychological distress. In contrast, among women, MI incidence increased with increasing psychological distress levels irrespective of age at baseline (Figure 3b). Similar sex and age patterns were observed for stroke (Figures 3c and 3d).

Psychological distress and relative risk of MI

Among men aged 45-79 years at baseline, moderate and high/very high distress were associated with 28% and 60% increased risk of MI after adjustment for sociodemographic factors, (HRs 1.28, 95% CI 1.15 to 1.43 and 1.60, 95% CI 1.39, 1.86, respectively; Table 4, model 2). Similar results were observed for women, although the effect estimate for moderate versus low/no psychological distress was not statistically significant (Table 4, model 2). Additional adjustment for lifestyle, disease history and clinical risk factors attenuated estimates further and in some instances estimates were no longer statistically significant. However, even in the fully adjusted models, a significant association or trend towards an association persisted (Table 4; models 3 and 4).

Among men aged 80 years or over the effect of psychological distress on MI risk was weaker (Table 4), with evidence of interaction on both the multiplicative scale (p-value for age-by-distress interaction: 0.003) and additive scales.

There was no evidence of any interaction between age and psychological distress among women, with effect estimates broadly similar across both age groups.

We did find evidence of interaction on the additive scale between sex and psychological distress in the 45-79 years age group, with high/very high psychological distress and male sex having a supra-additive effect on MI risk. Essentially, the joint effect of high/very high psychological distress and male sex on MI risk was greater than we would expect based on their separate effects on MI risk. All interaction results are provided in supplementary Table 6.

Psychological distress and relative risk of stroke

There was a similar dose-dependent association between psychological distress and stroke, although point estimates were larger in women than men. After adjusting for sociodemographic factors, moderate and high/very high distress were associated with 14% and 37% increased risk of stroke among men (HR 1.14, 95% CI 0.98 to 1.32 and 1.37, 95% CI 1.10 to 1.69, respectively) and 31% and 81% increased risk of stroke among women (HR 1.31, 95% CI 1.11 to 1.55 and 1.81, 95% CI 1.46 to 2.23; Table 5, model 2). Effect estimates were similar across younger and older age groups. There was no clear evidence of interaction between psychological distress and sex or between psychological distress and age on stroke risk (supplementary Table 7), although as with MI, effect estimates among men aged 80 years or over were weaker than in younger ages.

Sensitivity analyses

The association between psychological distress and stroke was similar for ischaemic and haemorrhagic stroke, although smaller numbers of haemorrhagic stroke decreased precision (supplementary Figure 2).

Results of the complete-case analyses for MI and stroke are given in supplementary Tables 8 and 9.

DISCUSSION

Psychological distress has a strong, dose-dependent, positive association with MI and stroke risk in both men and women. There was some indication of possible sex differences. Among those aged 45-79, we observed a supra-additive interaction between psychological distress and male sex on MI risk (i.e. the joint effect of psychological distress and male sex on MI risk was greater than we would expect). Among women the magnitude of effect of psychological distress appeared greater for stroke than for MI. Furthermore, associations generally persisted despite adjustment for a wide range of confounding factors. To our knowledge, this is by far the largest study of psychological distress and incident CVD, including more than four times the number of MIs[16-18] and double the number of strokes included in previous published studies combined.[14, 15, 19] It is also one of just a handful of studies to examine whether the effect of psychological distress differs by sex and age.

There is a paucity of prospective studies relating psychological distress to subsequent risk of CVD and to our knowledge none have used the K10 to measure psychological distress. However, despite some inconsistencies with previous studies, our findings concur with the view that high psychological distress is independently associated with increased CVD risk, even after controlling for a wide range of covariates. Consistent with our findings for MI, two previous small studies reporting on psychological distress and MI risk with stratification by sex reported a greater magnitude of effect in men than women.[16, 18] Contrastingly, a third study found no clear evidence of an association between psychological distress and MI risk when those with coronary heart disease at baseline were excluded.[16] Our findings are somewhat consistent with results from previous studies linking measures of psychological distress to stroke risk[14, 15, 19], although two studies found significant associations with fatal but not non-fatal[15] or hospitalised[14] stroke. The only study of stroke which stratified by sex reported a consistent association between psychological distress and stroke among both men and women, which concurs with our findings.[19]

The findings from our study, along with those from the broader literature, suggest that psychological distress might operate partly through lifestyle behaviours, but also support the view that other mechanisms may exist. Disorders such as depression and anxiety are thought to induce patho-physiologic changes, including: alteration of the hypothalamic-pituitary-adrenal axis of the neuroendocrine system; activation of inflammatory processes (e.g. through release of pro-inflammatory cytokines); platelet hyperactivity; and endothelial dysfunction.[34-37] It is reasonable to postulate that symptoms of psychological distress might operate through the same mechanisms to increase CVD risk. Interestingly, although a different construct, psychosocial stress has been linked to increased amygdalar activity, which in turn was associated with increased cardiovascular (including stroke) event risk, potentially through increased bone-marrow activity (and release of inflammatory cells) and arterial inflammation.[38] Our finding of a consistent association between psychological distress and both ischaemic and haemorrhagic stroke suggests that the underlying mechanism(s) are likely to cause pathophysiologic changes common to both pathological stroke

types. It is interesting that, consistent with some previous studies, the association between psychological distress and MI risk appears stronger in men than women. Whilst common mental disorders and psychological distress are more common in women than men, women are more likely than men to seek primary care for mental (as well as physical) health problems. Women might therefore address their mental health concerns more constructively than men, thereby partially negating the physical disease consequences of psychological distress. Somewhat paradoxically, we didn't find the same sex difference for stroke, with the risk perhaps slightly stronger in women than men. Effect estimates in women were however certainly larger for stroke than MI, raising the possibility of different pathways between psychological distress and types of CVD in women. Alternatively, these findings might reflect divergent protective effects of hormone levels on coronary heart disease as compared to cerebrovascular disease risk in women.[39] The apparent moderating effect of older age on the association between psychological distress and CVD risk in men may be more likely to be due to survival bias rather than a true counteraction of risk by older age. Men who survive into their 80s (and with symptoms of psychological distress) are perhaps a somewhat selected resilient sub-group. One might also query the role of non-CVD death as a potential competing risk in our analyses, which might affect/prevent the outcomes of interest being observed. However, in line with guidance on accounting for competing risks when addressing aetiological research questions, we did not calculate sub-distribution HRs to examine the role of non-stroke/non-MI death as a competing risk.[40, 41] As recommended, we additionally calculated cause-specific hazard ratios for non-stroke and non-MI death (data available on request). As expected, increased psychological distress was associated with increased risk of non-CVD death.

Whilst evidence from human and animal studies provide some support for a causal association between psychological distress and physical diseases such as MI and stroke, this remains a complex and contentious area. Alternative explanations for the observed associations include residual confounding, reverse causation, and common cause(s) leading to a spurious association. Whilst some degree of residual confounding is always possible, particularly by unknown confounders, the

magnitude of the observed associations in the present study, even after adjusting for confounding factors (some of which may actually lie on the causal pathway) suggests that residual confounding is unlikely to fully explain the observed associations. The association may be due to reverse causation, whereby psychological distress as a result of subclinical disease manifests prior to stroke event. Future research should address the issue of reverse causation using data from studies in which psychological distress is measured early in life with repeat measurement over the life-course along with the reliable recording of CVD events. Finally, psychological distress and CVD might be different manifestations of the same underlying mechanism, with psychological distress manifesting prior to CVD occurrence (i.e. the 'common soil' hypothesis). Human and animal studies demonstrate that chronic stress for example may lead to both psychiatric and physical illness.[34]

Strengths and limitations

Our study benefits from key strengths. It included a large CVD-free study population and a large number of incident CVD events during follow-up, providing sufficient power to stratify by sex and age. We also identified CVD events objectively through hospital and mortality records. Furthermore, studies of psychological distress in relation to stroke risk are less than common than cardiovascular disease and so our study makes a large contribution to this area. Psychological distress was measured with a highly reliable and valid tool, which performs well when evaluated against present-state DSM-IV disorders, especially mood and anxiety disorders.[23-27, 42] K10 also out-performs the GHQ-12 questionnaire.[25, 43] Lastly, we were able to adjust for a wide range of potential confounders, including those less commonly adjusted for in previous studies on this topic.

Our study has some limitations. The participation rate in the 45 and Up Study is about 18% and given the nature of the 'healthy cohort effect', it's unlikely to be representative of the general NSW population aged 45 and over.[21] However, importantly, the cohort is very large and heterogeneous across collected variables. Thus, whilst people with psychological distress may well be under-represented in this cohort, it is unlikely to have impacted internal comparisons of exposure and outcomes.[21] Information on psychological distress was missing for some participants, but exclusion

of these may, if anything, have underestimated the associations between psychological distress and CVD risk. Whilst record linkage to hospital admissions and mortality records facilitated robust outcome ascertainment, we may not have identified all CVD events. We would have missed events occurring outside NSW and the ACT or Australia itself, although these are likely to be few in number. We would have also missed non-hospitalised CVD events, which is more likely to have impacted on stroke, rather than MI, ascertainment. Based on Australian stroke incidence studies, around 15% of all strokes are not hospitalised, with the number likely to be higher among older people.[44] However, this would only have impacted the hazard ratios if hospitalisation for stroke was differentially associated with baseline psychological distress level, which is unlikely. It is possible that some non-strokes may have been misclassified as strokes and vice-versa, both within hospital and mortality records. A recent world-wide review of the accuracy of hospital and mortality records suggests that the use of appropriately selected, stroke-specific codes yields positive predictive values of greater than 70% in most studies and greater than 90% in some studies.[29] Again, misclassification of stroke diagnosis would only bias our findings if misdiagnosis was associated with baseline psychological distress level, which is unlikely. Finally, since we do not have time-varying information on psychological distress and covariates, we cannot be certain that the covariates are indeed confounders and not mediators in the relationship between psychological distress and CVD. We may therefore have over-adjusted our analyses by including possible mediators, thereby underestimating the association between psychological distress and CVD risk.

Implications

In the absence of clinical trials designed to examine long-term CVD outcomes among those treated for psychological distress symptoms (or indeed for diagnosed common mental disorders), further observational epidemiological research is needed in this area. Future research using studies with time-varying measures of psychological distress and covariates is needed to establish the contribution of potential mediating factors, including lifestyle factors and other less well-

understood, physiological mechanisms. This understanding would inform the design and success of preventive approaches aimed at reducing CVD risk in those suffering from psychological distress. Irrespective of the causal nature of the association between psychological distress and CVD, the growing evidence supports the need for renewed efforts: to encourage people with symptoms of psychological distress to seek medical help; for more active screening of, and better treatment for, psychological distress (and diagnosed common mental disorders); and to encourage screening for traditional cardiovascular risk factors in people with symptoms of psychological distress or diagnosed common mental disorders.

Conclusion

Psychological distress has a strong, dose-dependent, positive association with CVD risk in both men and women, but possible sex differences exist which deserve further investigation and replication in future studies. Confounding is unlikely to account for the observed associations, but further research is needed to determine causality and underlying mechanisms.

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DISCLOSURES

None

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Figure legends

Figure 1 Diagram depicting, in part A, possible pathways through which psychological distress might affect risk of cardiovascular disease and, in part B, potential confounders of the psychological distress-CVD association and the potential overlap between mediators and confounders

Figure 2 Flow diagram of included participants from the 45 and Up Study

Figure 3 Age-standardised incidence rates of MI among (a) men and (b) women and rates of stroke among (c) men and (d) women, by psychological distress level, stratified by age-group

507 Table 2 Baseline characteristics, by level of psychological distress, for all participants*

	Psychological distress		
	Low (N = 169,735)	Medium (N = 35,821)	High/very high (N = 16,121)
Characteristic	%	%	%
Age, years (mean ± SD)	61.8 ± 10.4	59.2 ± 10.2	58.2 ± 9.9
Categorical age, years			
40-59	48.4	61.0	66.1
60-69	29.8	23.4	21.2
70-79	14.6	10.0	7.6
80+	7.2	5.7	5.1
Female	52.6	57.7	59.9
Marital status			
Married/de facto	78.5	73.2	63.7
Divorced/separated/Widowed	16.0	19.3	25.7
Single	5.0	7.0	9.9
Geographical remoteness			
Major cities of Australia	49.5	49.8	50.1
Inner regional Australia	29.0	28.9	29.3
Outer regional Australia	6.8	7.2	7.4
Remote/very remote Australia	0.2	0.2	0.3
SEIFA index of relative disadvantage			
1 (least deprived)	21.6	18.5	13.9
2	19.8	20.0	19.3
3	20.0	20.1	20.4
4	19.9	20.8	21.9
5 (most deprived)	18.7	20.6	24.4
Education			
College/university degree	26.3	24.9	18.7
Certificate/diploma/trade or apprenticeship	32.8	32.4	30.4
High school certificate	9.9	9.9	10.0
School certificate	21.1	20.5	22.1

No qualifications	8.8	11.1	(17.2
Average household annual income per year (AUD)			
≥70,000	(28.1	25.2	16.6
50,000-69,999	11.7	11.6	9.2
40,000-49,999	7.7	7.6	6.9
30,000-39,999	8.3	8.0	7.4
20,000-29,999	9.1	9.6	9.7
≤19,999	15.2	19.3	29.8
BMI, kg/m^2 (mean ± SD)	26.9 ± 4.6	27.3 ± 5.2	27.9 ± 5.8
Missing	*6.7*	*7.2*	*8.3*
Smoking status			
Never	58.9	54.3	48.
Former	34.6	35.8	34.0
Current	6.0	9.4	16.9
Alcohol intake			
Moderate	38.0	36.6	31.0
None/rarely	29.4	33.0	41.1
Hazardous	24.8	22.1	17.3
Harmful	6.6	6.8	7.9
Physical activity			
Sufficiently active	80.1	74.7	66.4
Insufficiently active	14.2	17.7	21.2
Sedentary	3.1	4.7	8.2
Fruit and vegetable intake			
< 5 portions/week	66.2	69.4	69.5
Fish intake			
≥ twice/week	48.2	45.1	42.5
Once/week	40.3	40.9	39.3
Never	7.3	9.2	12.2
History of hypertension	33.0	33.5	35.7
History of heart disease	8.5	9.1	9.8
History of diabetes mellitus	7.1	8.4	11.3
Family history of stroke or heart disease	56.6	58.0	58.0

Treated for high cholesterol	13.2	14.3	16.2
Charlson comorbidity index			
0	92.0	89.7	86.8
1	4.5	5.8	7.9
2	1.8	2.2	2.5
≥3	1.7	2.3	2.8
WOMEN ONLY			
Menopausal status			
Pre-menopause	18.2	23.0	21.3
Post-menopause	51.0	44.0	40.6
Hysterectomy only	18.4	18.6	20.7
Bilateral oophorectomy post-menopause	1.6	1.6	1.6
Bilateral oophorectomy (surgical menopause)	6.1	6.8	8.0
Current HRT use	10.0	10.9	11.9
Current OCP use	0.3	0.3	0.4

AUD = Australian dollars; BMI = body mass index; HRT = hormone replacement therapy; OCP = oral contraceptive; SD = standard deviation

*Please see supplementary Table 3 for propotion of patients with missing information on each variable

Table 3 Sex-specific age-standardised incidence rates (per 1000 person-years) for myocardial infarction (MI) and stroke, by psychological distress level

	Men (N = 102,039)			Women (N = 119,638)		
Psychological distress	Person-years	MI events, n	MI rate, per 1000 person-years* (95% CI)	Person-years	MI events, n	MI rate, per 1000 person-years* (95% CI)
Low	376,443	2347	5.77 (5.53, 6.02)	420,984	1117	3.68 (3.42, 3.93)
Moderate	71,015	482	7.19 (6.52, 7.86)	97,951	244	4.09 (3.50, 4.68)
High/very high	29,549	242	9.28 (8.04, 10.53)	44,994	141	5.70 (4.60, 6.81)
	Person-years	Stroke events, n	Stroke rate, per 1000 person-years* (95% CI)	Person-years	Stroke events, n	Stroke rate, per 1000 person-years* (95% CI)
Low	377,895	1134	2.75 (2.58, 2.92)	421,217	704	2.64 (2.41, 2.87)
Moderate	71,391	204	3.34 (2.86, 3.82)	97,947	178	3.37 (2.80, 3.93)
High/very high	29,802	96	3.96 (3.11, 4.82)	45,028	105	5.07 (3.97, 6.17)

*Standardised to the sex-specific Australian Standard Population
CI = confidence interval; MI = myocardial infarction; n = number of MI/stroke events

Table 4 Serially adjusted hazard ratios for associations between moderate and high/very high psychological distress versus low distress and myocardial infarction, stratified by sex and age

	Psychological distress HR (95% CI)					
	All ages[*]		Aged 45-79[†]		Aged ≥80[‡]	
	Moderate	High/very high	Moderate	High/very high	Moderate	High/very high
MEN						
Model 1[§]	-	-	1.35 (1.21, 1.50)	1.84 (1.59, 2.12)	0.99 (0.78, 1.26)	1.11 (0.77, 1.60)
Model 2[||]	-	-	1.28 (1.15, 1.43)	1.60 (1.39, 1.86)	0.99 (0.78, 1.26)	1.12 (0.77, 1.62)
Model 3[#]	-	-	1.23 (1.10, 1.37)	1.39 (1.20, 1.62)	0.97 (0.76, 1.24)	1.09 (0.75, 1.58)
Model 4[**]	-	-	1.18 (1.06, 1.32)	1.30 (1.12, 1.51)	0.95 (0.74, 1.21)	1.02 (0.70, 1.49)
WOMEN						
Model 1[§]	1.16 (1.01, 1.34)	1.63 (1.37, 1.94)	1.18 (1.00, 1.40)	1.79 (1.45, 2.20)	1.11 (0.86, 1.43)	1.35 (0.97, 1.89)
Model 2[||]	1.11 (0.97, 1.28)	1.48 (1.23, 1.77)	1.12 (0.95, 1.33)	1.54 (1.25, 1.91)	1.09 (0.84, 1.41)	1.34 (0.95, 1.88)
Model 3[#]	1.05 (0.91, 1.21)	1.28 (1.07, 1.21)	1.05 (0.89, 1.25)	1.30 (1.05,1.61)	1.05 (0.81, 1.36)	1.24 (0.88, 1.75)
Model 4[**]	0.99 (0.86, 1.14)	1.18 (0.99, 1.42)	0.99 (0.84, 1.17)	1.19 (0.96, 1.47)	1.00 (0.77, 1.30)	1.18 (0.83, 1.66)

[*]Hazard ratios for all ages combined not reported for men since proportional hazards assumption violated
[†]number of myocardial infarctions / total, N: men = 2427 / 94,071; women = 1041 / 112,480
[‡]number of myocardial infarctions / total, N: men = 644 / 7968; women = 461 / 7158
[§]Adjusted for age
[||]Model 1 + adjustment for marital status, education, SIEFA index of disadvantage, household income, remoteness
[#]Model 2 + adjustment for smoking, alcohol intake, BMI, physical activity, fruit & vegetable intake, fish consumption
[**]Model 3 + adjustment for hypertension, diabetes, family history of stroke or heart disease and Charlson comorbidity index (in women, also adjusted for OCP use, HRT use and menopausal status)
HR = hazard ratio; CI = confidence interval

Table 5 Serially adjusted hazard ratios for associations between moderate and high/very high psychological distress versus low distress and stroke, stratified by sex and age

	Psychological distress HR (95% CI)					
	All ages		Aged 45-79[*]		Aged ≥80[†]	
	Moderate	High/very high	Moderate	High/very high	Moderate	High/very high
MEN						
Model 1[‡]	1.18 (1.02, 1.37)	1.50 (1.22, 1.85)	1.27 (1.06, 1.51)	1.65 (1.30, 2.09)	0.98 (0.73, 1.32)	1.16 (0.74, 1.80)
Model 2[§]	1.14 (0.98, 1.32)	1.37 (1.10, 1.69)	1.20 (1.01, 1.43)	1.44 (1.13, 1.84)	0.97 (0.72, 1.31)	1.12 (0.72, 1.74)
Model 3[||]	1.11 (0.95, 1.29)	1.27 (1.03, 1.57)	1.17 (0.98, 1.39)	1.32 (1.04, 1.69)	0.95 (0.71, 1.28)	1.09 (0.69, 1.70)
Model 4[#]	1.07 (0.92, 1.25)	1.19 (0.96, 1.48)	1.13 (0.94, 1.34)	1.24 (0.97, 1.59)	0.93 (0.69, 1.26)	1.01 (0.65, 1.59)
WOMEN						
Model 1[‡]	1.34 (1.13, 1.58)	1.89 (1.54, 2.32)	1.31 (1.06, 1.63)	1.83 (1.39, 2.40)	1.37 (1.06, 1.78)	1.99 (1.45, 2.73)
Model 2[§]	1.31 (1.11, 1.55)	1.81 (1.46, 2.23)	1.28 (1.03, 1.58)	1.68 (1.27, 2.22)	1.36 (1.05, 1.77)	1.96 (1.42, 2.71)
Model 3[||]	1.25 (1.06, 1.48)	1.64 (1.33, 2.03)	1.23 (0.99, 1.52)	1.52 (1.15, 2.02)	1.27 (0.97, 1.66)	1.75 (1.26, 2.43)
Model 4[#]	1.20 (1.02, 1.42)	1.56 (1.26, 1.93)	1.18 (0.95, 1.46)	1.44 (1.09, 1.92)	1.22 (0.93, 1.59)	1.66 (1.20, 2.31)

[*]number of strokes / total, N: men = 1007 / 94,071; women = 590 / 112,480
[†]number of strokes / total, N: men = 427 / 7968; women = 397 / 7158
[‡]Adjusted for age
[§]Model 1 + adjustment for marital status, education, SIEFA index of disadvantage, household income, remoteness
[||]Model 2 + adjustment for smoking, alcohol intake, BMI, physical activity, fruit & vegetable intake, fish consumption
[#]Model 3 + adjustment for hypertension, diabetes, family history of stroke or heart disease and Charlson comorbidity index (in women, also adjusted for OCP use, HRT use and menopausal status
HR = hazard ratio; CI = confidence interval

Figure 1

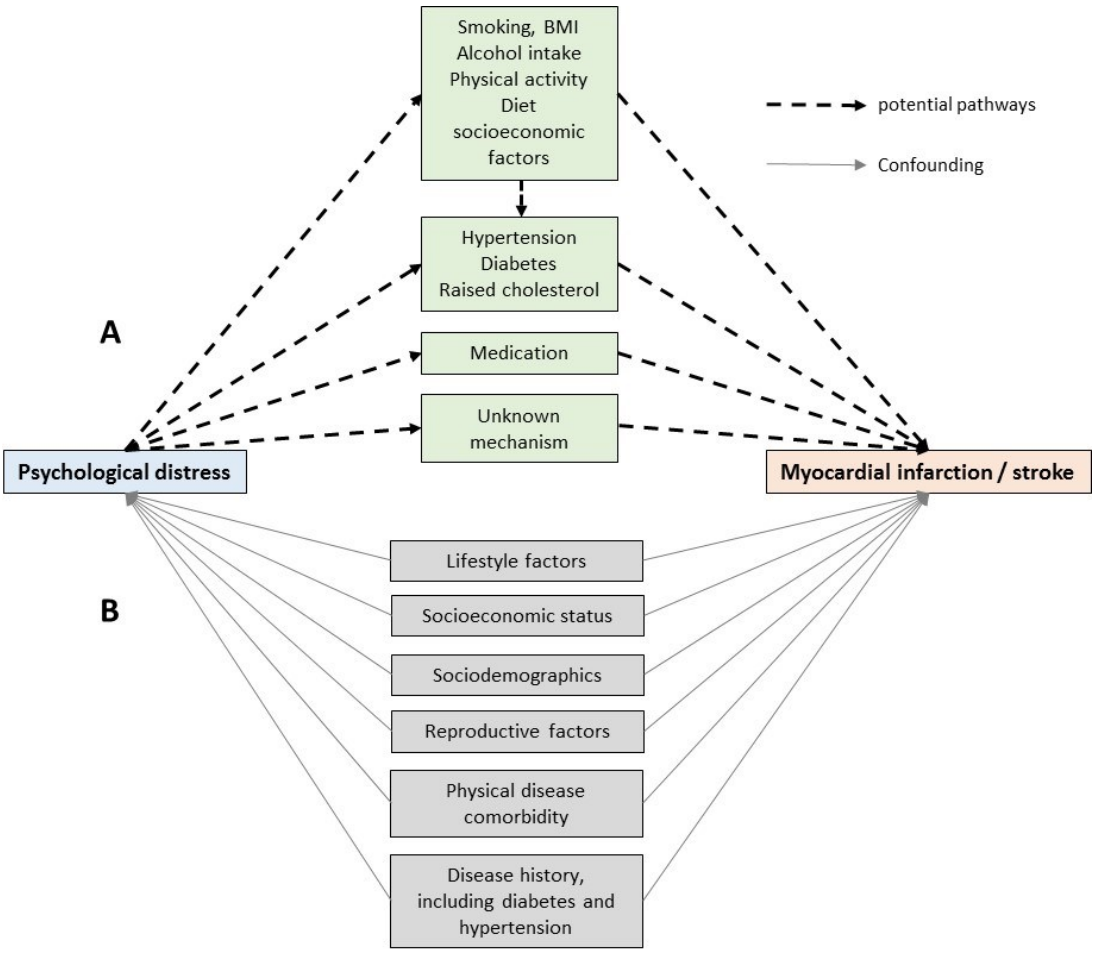

Smoking, BMI
Alcohol intake
Physical activity
Diet
socioeconomic factors
potential pathways
Confounding
Hypertension
Diabetes
Raised cholesterol
A
Medication
Unknown mechanism
Psychological distress
Myocardial infarction / stroke
Lifestyle factors
B
Socioeconomic status
Sociodemographics
Reproductive factors
Physical disease comorbidity
Disease history, including diabetes and hypertension

Figure 2

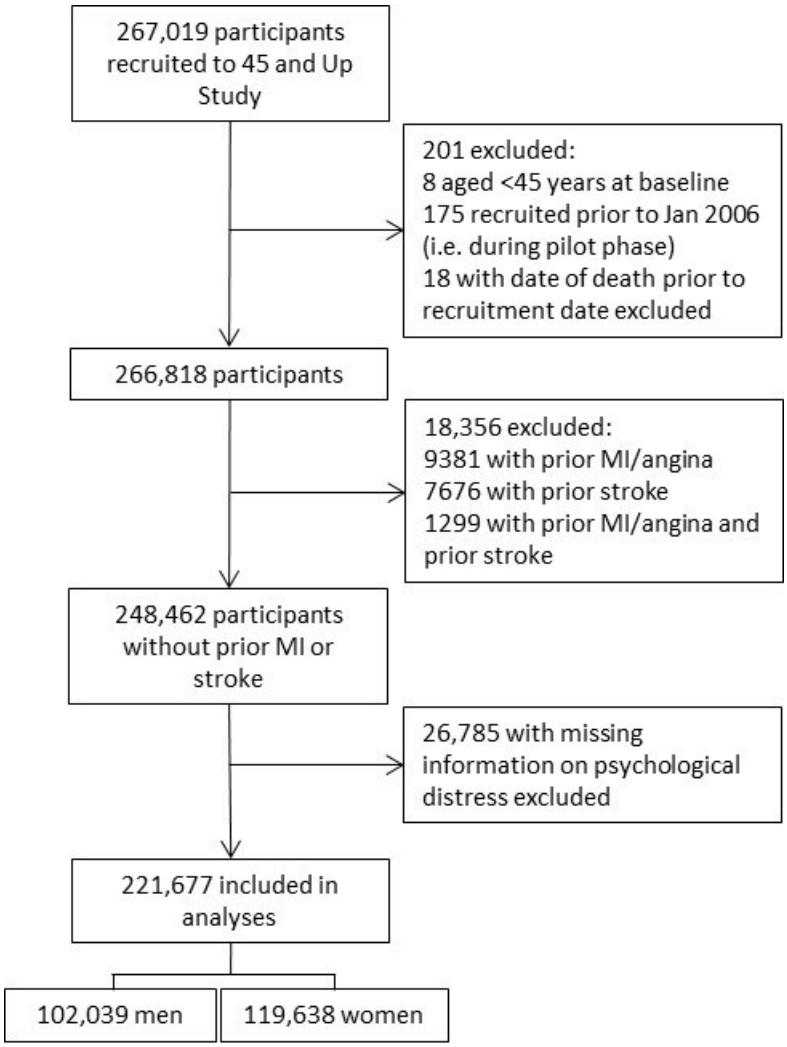
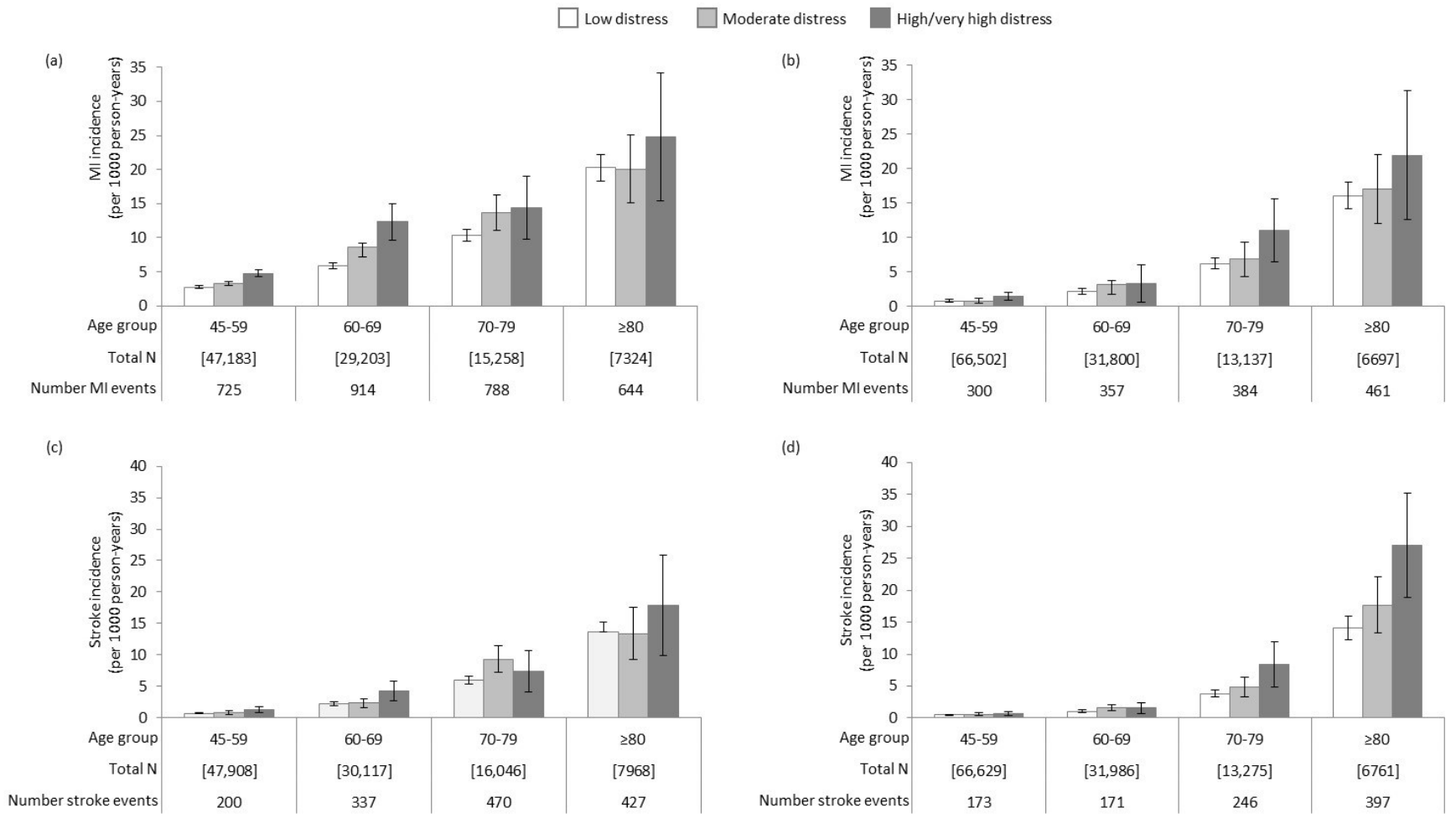

267,019 participants recruited to 45 and Up Study
201 excluded:
8 aged <45 years at baseline
175 recruited prior to Jan 2006 (i.e. during pilot phase)
18 with date of death prior to recruitment date excluded
266,818 participants
18,356 excluded:
9381 with prior MI/angina
7676 with prior stroke
1299 with prior MI/angina and prior stroke
248,462 participants without prior MI or stroke
26,785 with missing information on psychological distress excluded
221,677 included in analyses
102,039 men
119,638 women

Figure 3


Low distress
Moderate distress
High/very high distress
(a)
MI incidence (per 1000 person-years)
Age group 45-59 60-69 70-79 ≥80
Total N [47,183] [29,203] [15,258] [7324]
Number MI events 725 914 788 644
(b)
MI incidence (per 1000 person-years)
Age group 45-59 60-69 70-79 ≥80
Total N [66,502] [31,800] [13,137] [6697]
Number MI events 300 357 384 461
(c)
Stroke incidence (per 1000 person-years)
Age group 45-59 60-69 70-79 ≥80
Total N [47,908] [30,117] [16,046] [7968]
Number stroke events 200 337 470 427
(d)
Stroke incidence (per 1000 person-years)
Age group 45-59 60-69 70-79 ≥80
Total N [66,629] [31,986] [13,275] [6761]
Number stroke events 173 171 246 397